Complete Summary

GUIDELINE TITLE

Adjuvant systemic therapy for node-negative breast cancer.

BIBLIOGRAPHIC SOURCE(S)

Breast Cancer Disease Site Group. Adjuvant systemic therapy for node-negative breast cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 May 1 [online update]. 22 p. (Practice guideline report; no. 1-8). [79 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Node-negative breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations regarding the role of systemic adjuvant therapy for women with node-negative breast cancer

TARGET POPULATION

Women with node-negative breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Adjuvant Systemic Therapy

1. Tamoxifen
2. Chemotherapy regimens comprising cyclophosphamide (oral), methotrexate, and fluorouracil (CMF); methotrexate and fluorouracil (MF); cyclophosphamide, methotrexate, fluorouracil, and prednisone (CMFP); fluorouracil, epirubicin, and cyclophosphamide (FEC); cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF); or doxorubicin and cyclophosphamide (AC)
3. Chemotherapy plus tamoxifen

MAJOR OUTCOMES CONSIDERED

- Overall or disease-free survival
- Local recurrence
- Distant recurrence
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

1998 Guideline
A systematic search for practice guidelines, meta-analyses, and randomized trials was carried out through September 1996 using MEDLINE (from 1980) and CANCERLIT (from 1983). The search was updated in November 1997 and August 1998 using the medical subject heading (MeSH) "breast neoplasms/dt", the text words "node" and "negative", and "random:" as part of a text word, MeSH heading, or publication type. Use was also made of review articles, textbooks, and abstracts from major breast cancer meetings up to May 1998.

2003 Update
The literature search was revised to combine disease-specific text words and subject headings (breast, mammary, cancer, carcinoma, neoplasm[s], node[-]negative), treatment-specific terms (antineoplastic agents, chemotherapy, tamoxifen, hormonal therapy, antiestrogen, adjuvant, systemic therapy), and design-specific terms (meta-analysis, randomized controlled trial[s]). The literature search has been updated with the revised search terms using MEDLINE (through April 2003), the Cochrane Library (Issue 1, 2003), the Physician Data Query (PDQ) database and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1999-2002). The literature search was not restricted by language of publication.

Inclusion Criteria

1998 Guideline
The original guideline did not explicitly define inclusion criteria.

2003 Update
Articles were selected if they were:

1. Meta-analyses or randomized controlled trials comparing systemic adjuvant therapies in the treatment of women with node-negative breast cancer. Outcomes of interest included overall or disease-free survival, local recurrence, distant recurrence, or quality of life.
2. Evidence-based practice guidelines addressing the guideline questions were also included.

Both abstract and full reports were eligible.

NUMBER OF SOURCE DOCUMENTS

Two meta-analyses and 15 randomized controlled trials were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

1998 Guideline

A draft of the practice guideline report was discussed at the Breast Cancer Disease Site Group (DSG) meeting in April 1997. Feedback, particularly in two areas (i.e., definition of histologic grade and inclusion of lymphatic/vascular invasion as a poor prognostic factor) led to changes in the report. The report was discussed again at a DSG meeting in November 1997 and approved, on condition that minor refinements in the wording of the treatment recommendations be made.

At the Breast Cancer Disease Site Group (DSG) meeting of April 1998, the results of the practitioner feedback survey were discussed and addressed in the practice guideline report. The results of the 1995 Early Breast Cancer Trialists' meta-analysis had become available and were discussed and incorporated into the guideline report.

Some members of the Site Group felt that the results of the MA.5 trial that established the superiority of cyclophosphamide, epirubicin, fluorouracil (CEF) over cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in premenopausal, node-positive patients could be extrapolated to node-negative women.

The use of the combination of chemotherapy and tamoxifen was discussed at length. The results of National Surgical Adjuvant Breast and Bowel Project (NSABP) B-20 trial were reviewed, and their demonstration of the superiority of chemotherapy plus tamoxifen versus tamoxifen alone was found to be consistent with other trials. In the recently reported Intergroup study comparing tamoxifen with tamoxifen plus cyclophosphamide/doxorubicin/5-fluorouracil (CAF), in postmenopausal node-positive women the disease-free survival was 72% in the tamoxifen patients versus 79% in the CAFT patients ($p=0.01$). No difference was detected in survival. In the 1995 Early Breast Cancer Trialists' meta-analysis, the relative reduction in recurrence in the chemotherapy plus tamoxifen arm compared with tamoxifen alone was 19% (standard deviation [SD] 3) and for mortality 11% (SD 4) for women >50 years of age. The data for women <50years of age were 21% (SD 13) and 25% (SD 14), respectively. In summary, the evidence from the NSABP B-20 trial is consistent with the results of other studies comparing chemotherapy

plus tamoxifen versus tamoxifen alone in patients with node-positive breast cancer.

The 1995 Early Breast Cancer Trialists' meta-analysis detected a relative reduction in recurrence of 54% (SD 8) in women >50 years of age who received chemotherapy plus tamoxifen compared with chemotherapy alone and a reduction in mortality of 49% (SD 10) in this age group. The relative reductions for women <50 years were 40% (SD 19) for recurrence and 39% (SD 22) for mortality. (Note: The number of women in this subgroup was relatively small.)

If one accepts that the inclusion of chemotherapy provides an additional benefit to tamoxifen alone, then the question is which chemotherapy to use? In the NSABP B-19 trial, pre- and postmenopausal estrogen-receptor-negative, node-negative patients were randomized to MF for six months versus CMF for six months. The five-year disease-free survival (DFS) rate was 73% for the methotrexate, fluorouracil (MF) patients versus 82% for the CMF patients ($p<0.001$). The five-year survival rate was 85% in the former group compared with 88% in the latter group ($p=0.06$). There was increased toxicity in patients who received CMF. It is interesting to note that in the B-19 trial CMF was superior to MF. In the B-20, trial there has been no difference detected yet between CMFT patients and MFT patients. Of importance is the fact that there were mostly premenopausal women in the B-19 trial, whereas the B-20 trial included many postmenopausal women. It is conceivable that in the older women the toxicity of oral cyclophosphamide resulted in lower drug absorption and consequently, reduced effect from the inclusion of cyclophosphamide in this regimen. In the NSABP B-15 trial, CMF was compared with adriamycin and cyclophosphamide (AC) in node-positive patients, and no difference was detected in disease-free survival.

The DSG addressed the question of whether chemotherapy should be added for tamoxifen-responsive patients, and if so, whether to all subgroups. The agreement was that there was still a low-risk group for whom no adjuvant therapy should be recommended (e.g., <2 cm, all prognostic factors favourable). However, these women should be made aware that systemic therapy is offered to women at higher risk of recurrence.

The addition of chemotherapy to tamoxifen for high risk (>3 cm, or grade III) estrogen-receptor-positive postmenopausal women was also agreed upon. (Note: Tamoxifen is considered standard therapy in this situation based on a large body of evidence in node-negative and node-positive disease from the Early Breast Cancer Trialists' meta-analysis.) Reasonable chemotherapy regimens in this situation are CMF or adriamycin/cyclophosphamide (AC). Although AC was found to be equivalent to CMF in node-positive patients, its use in node-negative disease is by extrapolation. These two regimens have different toxicity profiles; for example, AC is associated with complete alopecia in all patients versus 40% occurrence in CMF patients. MF was

not favoured because of its observed inferiority in the NSABP B-19 trial.

The DSG agreed that in high risk (>3 cm, or grade III) estrogen-receptor-positive premenopausal women, chemotherapy would remain as the systemic adjuvant therapy of choice. There are insufficient data at the present time to recommend the addition of tamoxifen to chemotherapy in this subgroup. (The evidence from the Early Breast Cancer Trialists' meta-analysis is based on small numbers of patients and the results for survival are not statistically significant.) In addition, there is an ongoing clinical trial being conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) examining the additional benefit of tamoxifen after adjuvant chemotherapy in this subgroup of patients.

The DSG was less clear on what should be done with patients at moderate risk of recurrence. There was less enthusiasm for adding chemotherapy to tamoxifen for this group of patients compared to the high risk group. The moderate risk group would be an ideal group in which to evaluate a decision aid. If a decision board cannot be used, then tamoxifen should be recommended. However, these women should be made aware that chemotherapy plus tamoxifen is offered to women at higher risk of recurrence.

2003 Update
The information above remains current.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

In 1998, practitioner feedback was obtained through a mailed survey of 159 practitioners in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The

results of the survey were reviewed by the Breast Cancer Disease Site Group (DSG).

The guideline was approved by the Breast Cancer Disease Site Group and the Practice Guideline Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Choice of Therapy

- Pre- and postmenopausal women at minimal or low risk of recurrence (<2 cm, well-differentiated, and all other factors favourable or <1 cm, intermediate grade, and all other factors favourable) should receive no adjuvant systemic treatment. They should, however, be made aware that systemic therapy is offered to women at higher risk of recurrence.
- Premenopausal women (age <50 years) at moderate risk of recurrence (1-3 cm and intermediate grade or 2-3 cm and well-differentiated) and with estrogen-receptor-positive tumours should be offered tamoxifen. Chemotherapy added to tamoxifen may provide a modest incremental benefit over tamoxifen alone. This is an ideal situation for a decision aid.
- Premenopausal women (age <50 years) at high risk of recurrence (>3 cm, irrespective of any other factors, or >1 cm with either estrogen-receptor-negative, high grade or lymphatic/vascular invasion) should be offered chemotherapy. There are insufficient data at the present time to recommend the addition of tamoxifen to chemotherapy in this subgroup. If the patient refuses chemotherapy and the tumour is estrogen-receptor-positive, tamoxifen may be considered. There is insufficient data to determine the risk category of a tumour <1 cm in diameter associated with a poor prognostic factor (e.g., grade III, estrogen-receptor-negative, lymphatic/vascular invasion).
- Postmenopausal women (age >50 years) at high risk of recurrence (>3 cm, or >1 cm with high grade or lymphatic/vascular invasion) and with estrogen-receptor-positive tumours should be offered tamoxifen plus chemotherapy. The benefits and risks of additional chemotherapy should be discussed with the patient. If the patient refuses chemotherapy, then tamoxifen alone should be considered. Postmenopausal women at high risk of recurrence and with estrogen-receptor-negative tumours should be offered chemotherapy.
- Postmenopausal women (age >50 years) at moderate risk of recurrence (1-3 cm and intermediate grade, or 2-3 cm and well-differentiated) and with estrogen-receptor-positive tumours should be offered tamoxifen. Chemotherapy added to tamoxifen may provide a modest incremental benefit over

tamoxifen alone. This is an ideal situation for the use of a decision aid.

Duration of Tamoxifen

Hormonal therapy should consist of oral tamoxifen 20 mg daily for five years.

Chemotherapy Regimen

Polychemotherapy should reasonably comprise six cycles of cyclophosphamide (oral)/methotrexate/fluorouracil (CMF) or four cycles of doxorubicin/cyclophosphamide (AC).

Process of Decision-making

A patient with node-negative breast cancer should be informed of the availability of adjuvant systemic therapy and should be offered the opportunity of discussing such therapy with an expert clinician. She should be provided with detailed information concerning her risk of recurrence if untreated, the potential efficacy of adjuvant therapy in terms of recurrence and mortality, and the potential side effects of therapy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Two individual-patient-data meta-analyses were updated in August 2001. One analyzed data from 17,723 women involved in 47 randomized trials of long-term polychemotherapy versus no chemotherapy. The other was based on data from 55 randomized trials of tamoxifen versus no tamoxifen with a total of 37,099 participants.

- Adjuvant chemotherapy reduced the rate of disease recurrence (24% relative reduction in the annual hazard of recurrence compared with no chemotherapy) and improved survival (relative reduction in the annual hazard of death was 15%) in

women with breast cancer. Relative reductions in recurrence and death rates were similar for patients with node-negative and node-positive disease.

- Adjuvant tamoxifen reduced the rate of disease recurrence (26% relative reduction in the annual hazard of recurrence compared with no tamoxifen) and improved survival (relative reduction in the annual odds of death was 15%) in women with breast cancer. Relative reductions in recurrence and death rates were similar for patients with node-negative and node-positive disease but did vary by length of tamoxifen treatment. Relative reductions in recurrence rates were 18% with one year of tamoxifen, 25% with two years, and 42% with five years; relative reductions in death rates were 10% with one year of tamoxifen, 15% with two years, and 22% with five years.

POTENTIAL HARMS

Chemotherapy can be associated with a variety of adverse effects such as alopecia, nausea and vomiting, and infection. There are relatively few adverse effects associated with tamoxifen, but very rarely tamoxifen can cause venous thromboembolism or endometrial cancer.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Breast Cancer Disease Site Group. Adjuvant systemic therapy for node-negative breast cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 May 1 [online update]. 22 p. (Practice guideline report; no. 1-8). [79 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Nov 12 (updated online 2003 May 1)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Breast Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Breast Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The guideline developer instituted a new format for their guidelines and evidence summaries: A SUMMARY of the original Practice Guideline or Evidence Summary, integrated with the most current information, replaces the ABSTRACT, RECOMMENDATION, BRIEF REPORT and EVIDENCE UPDATE.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Adjuvant systemic therapy for node-negative breast cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2003 May. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This summary was updated by ECRI on December 23, 2002 and April 19, 2004. The information was verified by the guideline developer on April 29, 2004.

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Date Modified: 11/15/2004